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Percutaneous Interventions Alter the Hemostatic Profile of Patients With Unstable Versus Stable Angina

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Objectives. **The objectives of this study were to define the hemostatic profiles of patients with unstable angina compared with patients with stable angina and to investigate the effect of percutaneous interventions on the follow-up hemostatic profiles of these patients.**

Background. **Disturbances in hemostatic factors have been shown to be present in various clinical syndromes involving coronary artery disease. However, their role in stable angina versus unstable angina is less well defined.**

Methods. **We studied 61 patients with either stable or unstable angina undergoing percutaneous coronary interventions. Blood samples were drawn immediately before the intervention and at 1-month follow-up. Plasma levels of tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1) and von Willebrand factor (vWF) were measured by enzyme-linked immunosorbent assays.**

Results. **Patients with unstable angina had significantly higher t-PA levels (mean [±SE] 23.7 ± 3.4 vs. 14.3 ± 1.4 ng/ml, respectively, p = 0.02) and vWF antigen concentrations (2,231 ± 157 vs. 1,792 ± 108 mU/ml, respectively, p = 0.03) than patients with stable angina. No statistically significant differences were observed in the PAI-1 levels between the two groups (27.9 ± 5.5 vs. 21.4 ± 2.5 ng/ml, respectively, p = 0.25). At 1-month follow-up, there were no longer any significant differences in the t-PA or vWF levels between the two groups (15.7 ± 1.2 vs. 13.6 ± 0.6 ng/ml, p = 0.13; 1,962 ± 170 vs. 1,809 ± 88 mU/ml, p = 0.39, respectively). There were no significant differences between the hemostatic profiles of patients undergoing percutaneous transluminal coronary angioplasty or coronary stenting initially and at 1-month follow-up.**

Conclusions. **These data suggest that elevated plasma levels of t-PA and vWF may correlate with instability of atheromatous plaques, and that their decrease after coronary interventions may reflect plaque reendothelialization and stabilization.**

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Disturbances in the fibrinolytic system have been implicated in the pathogenesis and development of coronary artery disease (1,2). However, studies comparing the fibrinolytic profiles of patients with unstable angina to those with stable angina have shown conflicting results. Although some studies have shown levels of various factors to be more elevated in patients with unstable angina (3,4), others have shown no differences in the levels of these factors between patients with unstable angina and those with stable angina (5). Furthermore, there is scant data on the effect of percutaneous coronary interventions on the fibrinolytic system in patients with coronary artery disease.

We hypothesized that patients with unstable angina would have different hemostatic profiles from patients with stable angina and that successful percutaneous coronary interventions might alter these profiles. In this study, we demonstrate that the levels of tissue-type plasminogen activator (t-PA) and von Willebrand factor (vWF) antigens are higher in patients with unstable angina compared with those with stable angina, although there is no significant difference in the levels of plasminogen activator inhibitor-1 (PAI-1) antigen between the two groups. Furthermore, we demonstrate that, after successful percutaneous intervention by either balloon angioplasty or coronary stent placement, there is no longer any significant difference in the levels of t-PA and vWF antigens between the two groups.

Methods

This study was undertaken after approval by the Institutional Review Boards at Columbia–Presbyterian Medical Center and St. Francis Hospital.

Patient selection. Between July 1995 and April 1996, patients referred for percutaneous interventions to the cardiac catheterization laboratories at the participating hospitals were approached for enrollment in the study. A total of 61 patients were included in the study. Written, informed consent was obtained from all patients before their participation. Peripheral blood was withdrawn once at the start of the procedure

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Abbreviations and Acronyms

PAI-1 = plasminogen activator inhibitor-1
PTCA = percutaneous transluminal coronary angioplasty
t-PA = tissue-type plasminogen activator
vWF = von Willebrand factor

before heparin was given and again at 1-month follow-up. Seven patients were lost to follow-up, and these patients were excluded from the final analysis.

Exclusion criteria. Patients with a history of myocardial infarction documented by enzyme elevation within the previous 4 weeks were excluded. All patients with suspected hemostatic disorders, malignancy or inflammatory conditions were excluded.

Patient stratification. Patients were stratified to two groups based on their clinical presentation: 1) patients presenting with at least one episode of pain at rest lasting <20 min and associated with electrocardiographic changes and no evidence of myocardial infarction were classified as having unstable angina; and 2) patients with chronic exertional pain and no episodes of rest angina who were referred for elective angioplasty were classified as having stable angina.

Medications. After the procedure, each patient's medical regimen was determined by the referring cardiologist. However, all patients who had percutaneous transluminal coronary angioplasty (PTCA) received 325 mg of aspirin daily for at least 1 month, whereas patients with coronary stents received either 75 mg of dipyridamole three times a day, 325 mg of aspirin daily plus warfarin (Coumadin) or 325 mg of aspirin daily plus 250 mg of ticlopidine twice a day for 1 month.

Blood samples. The initial blood sample was withdrawn from the venous sheath before the start of the coronary intervention. The follow-up samples were obtained by venipuncture from the patients' forearm at 1 month. Each time 30 ml of blood was collected and divided into 10-ml tubes containing 1 ml of 3.13% sodium citrate. The plasma was separated by centrifugation at 3,000 rpm for 15 min and frozen at −70° until it was assayed for hemostatic factors.

Hemostatic system. The concentrations of t-PA, PAI-1 and vWF antigens were measured by commercially available immunoassay kits (American Diagnostica), as previously described (6).

Statistics. Patients were divided into two groups for analysis: those with unstable angina and those with stable angina. Baseline characteristics of the patients were compared using the unpaired *t* test for continuous variables and the chi-square test for discrete variables. The significance of the correlation between t-PA and vWF levels and cholesterol was measured using the z test. Because the data were not distributed normally, the Mann-Whitney *U* test was used to compare t-PA, PAI-1 and vWF antigens between the two groups. The Mann-Whitney *U* test was also used to compare hemostatic factors in patients who had PTCA versus coronary stent placement.

Table 1. Baseline Clinical Characteristics of Patients With Stable and Unstable Angina

	Unstable Angina (n = 18)	Stable Angina (n = 43)	p Value*
Age (yr)	60 ± 13	62 ± 9	NS
Gender (M/F)	14/4	38/5	NS
Risk factors			
Hypertension	13 (72)	31 (72)	NS
Smoking	3 (17)	7 (16)	NS
Diabetes	7 (39)	10 (23)	NS
Hyperlipidemia	12 (67)	23 (53)	NS
Medications			
Aspirin	18 (100)	43 (100)	NS
Beta-blocker	10 (56)	29 (67)	NS
Heparin	11 (61)	10 (23)	0.005
ACE inhibitor	6 (33)	8 (19)	NS
Nitroglycerin	13 (72)	13 (27)	0.003
Low EF, <40%	7 (39)	8 (19)	NS
WBC (10^9/liters)	8 ± 1.7	9 ± 2	NS
Multivessel disease	6 (33)	14 (33)	NS
Cholesterol (mg/dl)	216 ± 50	193 ± 38	0.05
Triglycerides (mg/dl)	207 ± 107	191 ± 126	NS

*Unstable versus stable angina. Data are presented as mean value ± SD or number (%) of patients. ACE = angiotensin-converting enzyme; EF = ejection fraction; NS = not significant; WBC = white blood cell count.

Results are expressed as mean ± SE. Statistical significance was defined as $p < 0.05$.

Results

The differences in the baseline characteristics between the two groups are presented in Table 1. Patients with unstable angina were more likely to be taking heparin or nitroglycerin. Patients with unstable angina also had higher cholesterol levels. The initial and 1-month follow-up values of the plasma hemostatic factors are shown in Table 2. The mean value of the t-PA antigen levels was higher in patients with unstable angina compared with patients with stable angina at the time of the percutaneous intervention (mean [±SE] 23.7 ± 3.4 vs. 14.3 ±

Table 2. Values of Tissue-Type Plasminogen Activator, von Willebrand Factor and Plasminogen Activator Inhibitor-1 in Patients With Stable Versus Unstable Angina

	Unstable Angina	Stable Angina	p Value
Initial values			
t-PA (ng/ml)	23.7 ± 3.4	14.3 ± 1.4	0.02
vWF (mU/ml)	2,231 ± 157	1,792 ± 108	0.03
PAI-1 (ng/ml)	27.9 ± 5.5	21.4 ± 2.5	NS
Follow-up values			
t-PA (ng/ml)	15.7 ± 1.2	13.6 ± 0.6	NS
vWF (mU/ml)	1,962 ± 170	1,809 ± 88	NS
PAI-1 (ng/ml)	31.6 ± 5.7	29.4 ± 3.3	NS

Data are expressed as mean value ± SE. NS = not significant; PAI-1 = plasminogen activator inhibitor-1; t-PA = tissue-type plasminogen activator; vWF = von Willebrand factor.

Table 3. Values of Tissue-Type Plasminogen Activator, von Willebrand Factor and Plasminogen Activator Inhibitor-1 in Patients Receiving Stents Versus Percutaneous Transluminal Coronary Angioplasty*

	Coronary Stents (n = 27)	PTCA (n = 34)
Initial values		
t-PA (ng/ml)	14.5 ± 2.0	19.2 ± 2.1
vWF (mU/ml)	1,933 ± 133	1,912 ± 129
PAI-1 (ng/ml)	22.2 ± 3.0	24.1 ± 3.5
Follow-up values		
t-PA (ng/ml)	15.3 ± 0.8	13.3 ± 0.8
vWF (mU/ml)	1,855 ± 144	1,853 ± 84
PAI-1 (ng/ml)	33.1 ± 4.6	27.7 ± 3.5

*p = NS for all comparisons. Data are expressed as mean value ± SE. PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 2.

1.4 ng/ml). The mean value of vWF antigen levels was also higher in patients with unstable angina compared with patients with stable angina (2,231 ± 157 vs. 1,792 ± 108 mU/ml). The difference between the unstable angina and stable angina groups was significant for t-PA (p = 0.02) as well as for vWF (p = 0.03). However, there were no significant differences in the PAI-1 antigen levels between the two groups (27.9 ± 5.5 vs. 21.4 ± 2.5 ng/ml, p = 0.25). When cholesterol levels were compared with t-PA and vWF antigen levels, no significant correlation was demonstrated (data not shown).

At 1-month follow-up, there were no longer any significant differences in the values of t-PA between the unstable angina and stable angina groups (15.7 ± 1.2 vs. 13.6 ± 0.6 ng/ml, respectively, p = 0.13). The values of vWF were also no longer significantly different between the unstable and stable angina groups (1,962 ± 170 vs. 1,809 ± 88 mU/ml, respectively, p = 0.39). At the time of 1-month follow-up, 12 patients had recurrent angina (3 with unstable angina and 9 with stable angina).

The values of hemostatic factors in patients receiving coronary stents (n = 27) were compared with those of patients who underwent PTCA only (n = 34). Twenty-two patients with stable angina had PTCA, whereas 21 patients had coronary stent placement. Among patients with unstable angina, 11 had PTCA and 7 received coronary stents. The initial and follow-up values of hemostatic factors in these patients are shown in Table 3. There were no differences in any of the hemostatic factors in the study patients based on the type of percutaneous coronary intervention used.

Discussion

We determined the levels of t-PA, PAI-1 and vWF antigens in patients with unstable and stable angina undergoing coronary angiography and percutaneous coronary interventions. There were significant elevations of t-PA and vWF antigen levels in patients with unstable angina compared with those with stable angina. However, no significant differences were observed in the PAI-1 antigen levels between the two groups. Furthermore, we monitored these patients 1 month after percutaneous coronary interventions and demonstrated for the first time that, after successful intervention with either PTCA or coronary stent placement, there were no longer any differences between the levels of t-PA and vWF antigens between the two groups.

von Willebrand factor in angina pectoris. This factor is synthesized by endothelial cells and megakaryocytes (7,8). It is essential both for platelet adhesion and aggregation. Insults to endothelial integrity result in release of vWF into the blood. Disease processes involving endothelial cell injury have been shown to have elevated levels of vWF (9). Unstable angina is the result of plaque rupture and subsequent exposure of the subendothelial contents to the blood (10). As plaques rupture, the damaged endothelial cells release vWF, which may account for the elevated vWF antigen levels in this study. It has also been demonstrated that vWF levels are increased in conditions involving intravascular clot formation (11). Therefore, elevated levels of vWF in our study could also be a marker of thrombus formation at the site of plaque rupture.

Tissue-type plasminogen activator in angina pectoris. Elevated serum t-PA levels have been demonstrated in cardiovascular conditions involving endothelial cell damage (12). Levels of t-PA are also increased in conditions involving intravascular thrombus formation (13). In unstable angina, elevated t-PA antigen levels may be the result of endothelial cell damage and thrombus formation at the site of plaque rupture. Elevated levels of t-PA antigen might seem paradoxic at first. However, most of the t-PA in the plasma travels while bound to PAI-1 molecules (14). As such, the increased t-PA levels reflect circulating t-PA–PAI-1 complexes that are inactive and therefore markers of attenuated rather than enhanced fibrinolytic activity (15).

Effect of percutaneous coronary interventions on hemostatic factors. We observed that after balloon angioplasty or stent placement, the levels of t-PA and vWF were no longer distinguishable between the two groups. In the pig model of balloon angioplasty, regrowth of endothelium over the injury site is complete 7 days after the procedure (16). It has also been demonstrated in swine models of stent placement that stents are completely covered by regenerated endothelium 28 days after stent deployment (17,18). As healthy endothelium covers the plaque region, it is reasonable to postulate that t-PA and vWF antigen levels should decrease. Therefore, the attenuation of these factors after the intervention in the unstable angina group could reflect reemergence of healthy endothelium as well as plaque stabilization and quiescence.

Conclusions. Serum levels of t-PA and vWF antigens are elevated in patients with unstable angina compared with those with stable angina. These differences are no longer present 1 month after a successful percutaneous coronary intervention—either balloon angioplasty or coronary stent placement—which may represent plaque reendothelialization as well as stabilization.

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